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Introduction

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Perry's *Chemical Engineer's Handbook* (1) defines the granulation process as "any process whereby small particles are gathered into larger, permanent masses in which the original particles can still be identified." This definition is of course particularly appropriate to a pharmaceutical granulation where the rapid breakdown of agglomerates is important to maximize the available surface area and aid in solution of the active drug. The granulation process of size enlargement used within the pharmaceutical industry has its roots in ancient times. The practice of delivering medicinal powder by hand rolling into a pill by using honey or sugar has been used for centuries. It is still the practice to deliver the botanical and herbal extract in homeopathic and ayurvedic branches of medicine, which are still practiced in India along with allopathic medicine. The term "granulated" material is derived from the Latin word "granulatum," meaning grained. The granulated material can be obtained by direct size enlargement of primary particles, or size reduction from dry compacted material. In modern times, granulation technology has been widely used by a wide range of industries, such as coal, mining, and agrochemical. These industries employ agglomeration techniques to reduce dust, provide ease of handling, and enhance the material's ultimate utility.

The development of pharmaceutical granulation was driven by the invention of the tablet press by W. Brockedon in 1843. Subsequent improvements in the tablet machinery were patented in the United States by J. A. McFerran (1874), T. J. Young (1874), and J. Dunton (1876). The demands on the granulation properties were further enhanced in the 1970s as high-speed tablet and capsule filling machines with automated controls were introduced. The continuous refinements in the regulatory requirements such as low-dose products requiring blend uniformity/content uniformity necessitated knowledge and technology to produce the required granule characteristics. The high-speed compression and capsule filling machines require a uniform flow of material to the dies or filling stations that produce pharmaceutical dosage form.

Granulation is an example of particle design. The desired attributes of the granule are controlled by a combination of the formulation and the process.

Granulation methods can be divided into two major types: wet methods which utilize some form of liquid to bind the primary particles, and dry methods which do not utilize any liquid (Fig. 1).

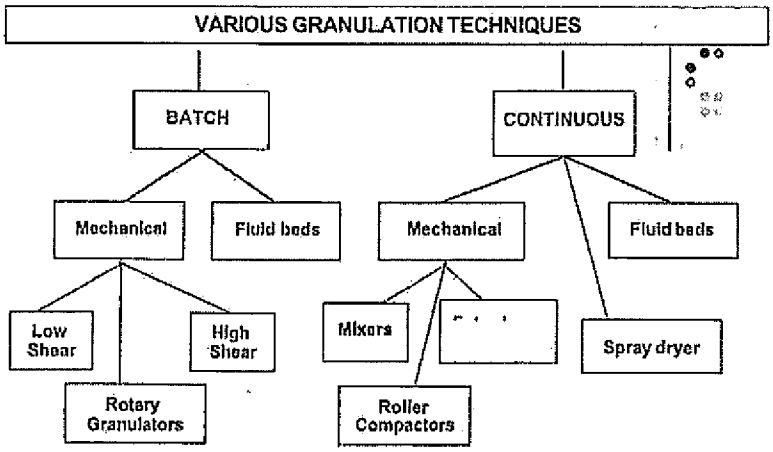

Figure 1 Various granulation techniques

Application of spray dryer to produce granulated product suitable for direct compression is now possible.

A new approach in the 1990s was to use supercritical fluid technology to produce uniform particles to replace crystallization. Even though super critical fluids were discovered over 100 years ago, and the commercial plant was built over 20 years ago in the United States, it is only now that the technology is used for a number of pharmaceutical applications (2–5), so as to produce aspirin, caffeine, ibuprofen, acetaminophen, etc. One of the major areas on which the research and development of supercritical fluids is focused is particle design. There are different concepts such as "rapid expansion of supercritical solution," "gas antisolvent recrystallization," and "supercritical antisolvent" to generate particles, microspheres, microcapsules, liposomes, or other dispersed materials.

When the supercritical fluid and drug solution make contact, a volume expansion occurs leading to a reduction in solvent capacity, increase in solute saturation, and then supersaturation with associated nucleation and particle formation. A number of advantages are claimed by using this platform technology (6), such as particle formation from nanometers to tens of micrometers, low residual solvent levels in products, preparation of polymorphic forms of drug, etc.

The classical granulation process using either wet or dry methods is employed in the process industries. Pharmaceutical granulation process is used for tablet and sometimes capsule dosage forms; however, in some applications the process is used to produce spherical granules for the modified release indications or to prepare granules as sprinkles to be used by pediatric patients. In some countries like Japan, having granulated product in a "sachet" is acceptable where a large dose of the drug product is not suitable for swallowing. The reasons for granulating a pharmaceutical compound are listed as follows:

1. To increase the uniformity of drug distribution in the product
2. To densify the material
3. To enhance the flow rates and rate uniformity
4. To facilitate metering or volumetric dispensing

5. To reduce dust
6. To improve the appearance of the product.

Five primary methods exist to form an agglomerated granule. They are formation of solid bridges, sintering, chemical reaction, crystallization, or deposition of colloidal particles. Binding can also be achieved through adhesion and cohesion forces in highly viscous binders.

Successful processing for the agglomeration of primary particles depends on proper control of the adhesional forces between particles, which encourage agglomerate formation and growth and provide adequate mechanical strength in the product. Furthermore, the rheology of the particulate system can be critical to the rearrangement of particles necessary to permit densification of the agglomerate and the development of an agglomerate structure appropriate for the end-use requirements. If the particles are close enough then the surface forces such as van der Waals forces (short-range) and electrostatic forces can interact to bond particles. Decreasing particle size increases surface–mass ratio and favors the bonding. van der Waals forces are sevenfold stronger than electrostatic forces and increase substantially when the distance between them is reduced, which can be achieved by applying pressure as in dry granulation method.

The cohesive forces that operate during the moist agglomerates are mainly due to the liquid bridges that develop between the solid particles. Electrostatic forces keep particles in contact long enough for another mechanism to govern the agglomeration process.

The processing of drug substance with the excipients can be achieved without going through the granulation steps. By simply mixing in a blender, a directly compressible formulation can be processed and compressed in tablets or filled in the hard gelatin capsules. In the 1970s, microcrystalline cellulose as a directly compressible vehicle was introduced. The compressible formulation containing microcrystalline cellulose is suitable for a number of products. This has several obvious advantages, such as lower equipment cost, faster process time, and efficient operation involving only two process steps. Sometimes excipient costs may have to be compared against the savings in the processing steps and equipment by using alternate methods.

There are, however, a number of products that require low dose of drug substance, where the blend uniformity and the content uniformity in the drug product are critical. Traditionally, the assessment of the blend uniformity is done after the blending process is complete. This required considerable delays in obtaining results, and the sampling techniques and product discharge from the blender required consistency to obtain satisfactory results. However, with the current interest in process analytical technology (PAT) on-line measurement of ingredients is possible. The U.S. Food and Drug Administration (FDA) has recently released guidance for industry detailing the current thinking on PAT (7).

Other than content uniformity of a low-dose drug substance there are a number of reasons why direct compression may not be suitable for a wide array of products. These include the required flow properties; the amount of drug substance in a dosage form may require it to be densified to reduce the size of the drug product, obtain the required hardness, friability, disintegration/dissolution, and other attributes.

Another approach which is becoming popular is to use traditional spray-drying process to produce drum to hopper granulation by-passing the conventional granulation process. This process may be suitable for large-volume products such as over-the-counter tablets or capsules.

Dry compaction technique like roller compaction is experiencing renewed interest in the industry. There are a number of drug substances which are moisture sensitive and cannot be directly compressed. The roller compaction provides suitable alternative technology for processing these products.

Early stages of wet granulation technology development, employed low-shear mixers or the mixers/blenders normally used for dry blending such as ribbon mixers. There are a number of products currently manufactured using these low-shear granulators. The process control and efficiency has increased over the years; however, the industry has embraced high-shear granulators for wet granulation because of its efficient and reproducible process and modern process control capabilities. The high-shear mixers have also facilitated new technologies, such as one-pot processing, that use the mixer to granulate and then dry using vacuum, gas stripping/vacuum, or microwave assist in the same vessel.

Fluid-bed processors have been used in the pharmaceutical industry for the last 35 years, initially only as a dryer, and now as a multiprocessor to granulate, dry, pelletize, and coat particles. The most preferred method of granulation is to use the high-shear mixer to granulate and use the fluid bed as a dryer in an integrated equipment setup. This provides the best of both technologies: efficient controllable dense wet granules and a fast drying cycle using fluid-bed dryer. Here again, the choice of this approach will be dependent on the product being processed, and its desired properties at the end of the granulation process. Extrusion/spheronization is used to produce granulation for the tableting or pelletizing, which involves mixing, extruding, spheronizing, and drying unit operations. These pellets can be produced as matrix pellets with the appropriate polymer or are coated in fluid-bed unit to produce modified release dosage forms. Table 1 illustrates various options to granulate a pharmaceutical compound.

Many researchers studied the influence of material properties of the granulating powder and process conditions on the granulation process in a rather empirical way. In the 1990s a fundamental approach to research was started on various topics in the granulation research, looking into more detailed aspects of particle wetting,

Table 1 Frequently Used Granulation Techniques and Subsequent Processing

	Process	Drying technique
Wet granulation	Low-shear mixer	Tray or fluid-bed dryer
	High-shear mixer	Tray or fluid-bed dryer
	High-shear mixer	Vacuum/gas stripping/microwave assist—one-pot
	Fluid-bed granulator/dryer	Fluid-bed granulator/dryer
	Spray dryer	Spray dryer
	Extrusion/spheronization	Tray or fluid-bed dryer
	Continuous mixer granulator (mechanical)	Fluid bed—continuous or batch
	Continuous fluid-bed granulator	Fluid bed (continuous)
Dry granulation	Process	Further processing
	Direct compression	Blend and process further
	Slugging	Mill slugged tablets/blend/recompress/process further
	Roller compactor	Compacts milled/blend/process further

mechanism of granulation, material properties, and influence of mixing apparatus on the product. The overall hypothesis suggested that the granulation can he predicted from the raw material properties and the processing conditions of the granulation process. One of the major difficulties encountered in granulation technology is the incomplete description of the behavior of powders in general. The ongoing fundamental research on mixing, segregation mechanisms of powder, surface chemistry, and material science are necessary to develop the theoretical framework of granulation technology. An excellent review of the wet granulation process was presented by Iveson and coauthors (8). The authors have advanced the understanding of the granulation process by stating that there are three fundamental sets of rate processes which are important in determining wet granulation behavior. These are wetting and nucleation, consolidation and growth; and breakage and attrition. Once these processes are sufficiently understood, then it will he possible to predict the effect of formulation properties, equipment type, and operating conditions of granulation behavior, provided these can be adequately characterized according to the reviewers.

Efficient and cost-effective manufacturing of pharmaceutical products is being evaluated by the scientists, engineers, and operational managers of pharmaceutical companies worldwide. In the United States, where 49% of the world pharmaceutical market is, pharmaceutical companies are under tremendous pressure from the managed care organizations, politicians, and consumers. The pharmaceutical industry, worldwide in general and in the United States in particular, faces a unique paradox—drive future innovation through substantial R&D investments and return competitive margin to shareholders, while providing access to pharmaceutical products at low or no cost. The industry has reached a critical juncture in its 100-year history. The industry is impacted simultaneously by growing competition, declining market performance, increasing regulation, escalating pricing pressures, and rapidly evolving innovations for improving people's health and quality of life. A new report (9) into pharmaceutical R&D has identified an emerging trend favoring outsourcing of discovery, research, clinical trials, and manufacturing of dosage forms, providing relief from the consistent, high-growth financial return faced by the majority of pharmaceutical companies. Outsourcing allows these companies to pursue potential new revenue streams outside of their core focus areas, and to benefit from improved productivity, emerging technologies, inlicensing opportunities, and increased growth. Consumers and local governments in the United States are pressuring the FDA authorities and politicians to allow importation of the drugs from other countries like Mexico and Canada where costs are generally lower than in the United States. Demands for price control also extend to Europe; government-backed pharmaceutical payment plans in Germany and Italy, for example, have cut back reimbursements. Other European countries have controls on the drug prices. As a result of these pricing pressures and to enhance the drugs in the pipeline, mergers and acquisitions have accelerated. Acquisitions remain the preferred route to quickly enhance a product portfolio. This trend of merging of equals or takeover of the significant technological companies will continue. This has created emergence of small niche technology companies as well. Major pharmaceutical companies are witnessing the end of traditional research and development. Drug delivery companies are becoming potential targets for mergers or strategic alliances. During all of the upheaval that the industry is going through, it is becoming obvious that the cost of development and production, and cost of goods, must he controlled. Recently released draft guidance by the U.S. FDA for quality systems approach for the current good manufacturing practices may help to streamline the

compliance programs in the industry (10). The efficiencies in the research, development, and manufacturing, which were not necessarily sought after, are becoming the first priority of the pharmaceutical companies however small they may he in comparison to the final cost of the product to consumer. The manufacturing of solid dosage product is no exception.

The significant advances that have taken place in the pharmaceutical granulation technology are presented in this book to provide the readers with choices that are available. There is no substitute for good science. The characterization of the drug substance along with the knowledge of granulation theory, process modeling capability, in-line or on-line (PAT) tools, process scale-up approaches, and a good definition of the end product required will prepare the reader to explore the various options presented in this book. Each drug substance poses a unique challenge that must be taken into consideration at the process selection stage by the scientists. The various techniques presented in this book will further help the scientists in their understanding and selection of the granulation process most appropriate for the drug substance. For production engineering, validation, and quality professionals in the industry, this book is intended to provide the fundamental understanding of the technique of granulation, and the rationale behind the selection of each particular technique. This will further enhance the ability to design the production plant, carry out the technology transfer, scale-up, troubleshoot, and maintain the pharmaceutical granulation operation, in accordance with regulatory compliance.

REFERENCES

1. Ennis BJ, Litster JD. Particle enlargement. Perry RH, Greens D, eds. Perry's Chemical Engineer's Handbook. 7th ed. New York: McGraw Hill, 1997:20-56–20-89.
2. Charoenchaitrakool M, Dehghani F, Foster NR. Micronization by RESS to enhance the dissolution rates of poorly water soluble pharmaceuticals. Proceedings of the 5th International Symposium on Supercritical Fluids, Atlanta, GA, April 8–12, 2000.
3. Matson DW, Fulton JL, Petersen RC, Smith RD. Rapid expansion of supercritical fluid solutions: solute formation of powders, thin films, and fibers. Ind Eng Chem Res 1987; 26:2298–2306.
4. Subra P, Boissinot P, Benzaghou S. Precipitation of pure and mixed caffeine and anthracene by rapid expansion of supercritical solutions. Proceedings of the 5th Meeting on Supercritical Fluids, Tome I, Nice, France, March 23–25, 1998.
5. Gilbert DJ, Palakodaty S, Sloan R, York V. Particle engineering for pharmaceutical applications—a process scale up. Proceedings of the 5th International Symposium on Supercritical Fluids, Atlanta, GA, April 8–12, 2000.
6. York P, et al. Supercritical fluids ease drug delivery. Manuf Chemist 2000: 26–29.
7. Food and Drug Administration. Guidance for Industry PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance. FDA, September 2004.
8. Iveson SM, Litster JD, Hopgood K, Ennis B. Nucleation, growth, and breakage phenomenon in agitated wet granulation process: a review. Powder Technol 2001; 117:3–39.
9. Cambridge Healthcare Advisors (CHA) Report. Report identifiesincreasing outsourcing by pharma–Inpharma.com, September 29, 2004.
10. Guidance for Industry. Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations, Draft Guidance, September 2004.